AMENDMENT

In the claims:

Please amend claim 8 as follows:

Claims 1- 7 (cancelled)

Claim 8 (currently amended). An isolated murine embryonic stem cell line comprising an engineered mutagenic sequence in a gene comprising the [an] exon sequence disclosed in SEQ ID NO:328.

Claim 9 (cancelled)

SUMMARY OF THE INVENTION

The Human genome has been sequenced and the published analysis has determined that only a small fraction of the genome encodes exon sequence that can be spliced, polyadenylated, and translated to produce protein. As each gene is identified and bioinformatically annotated with standard homology and expression data, the scientific community decides where next to proceed. A variety of *in vitro* approaches are available; however, *in vivo* systems provide insights into gene function within a physiological context. More particularly, mammalian *in vivo* systems (such as transgenics and knockouts) directly provide insights into gene function within the broader context of mammalian physiology.

From a pharmaceutical development perspective, discovering the physiological role of a gene (using the function of encoded protein, or potential drug "target," as a proxy) provides critical insights into the predicted therapeutic efficacy of a drug crafted to antagonize this target, *and* the predicted "on target" side-effect profile of this drug. The FDA regulatory "trash bins" historically include products that were rushed into development based on "known" *in vitro* and biochemical functions, but without the important preclinical credentials provided by *in vivo* indicators of drug action, specificity, and safety. These are precisely the kind of pharmaceutically relevant *in vivo* credentials provided by the described ES cells. The described genetically engineered ES cells can directly be used to produce mice capable of germline transmission of the genetically engineered allele using routine methods well known to those skilled in the art at the time the present application was filed (*i.e.*, microinjection of the ES cells to generate chimeric mice and subsequent breeding steps to produce mice having a genetically engineered mutation in the mutated and specifically identified gene). The resulting "knockout" mice can then be subject to a routine medical work-up to determine the function of the corresponding gene product (by discovering the physiological symptoms caused by its absence) in mammalian physiology. In the present instance, the described ES cells contain a genetically engineered mutation that inactivates the murine ortholog of a novel human RNA binding protein (see Protein accession no. NP_006858). More significantly, knockout mice produced using these mutated ES cells display an overt phenotype of reduced viability marked by hydronephrosis of the kidneys as well as a variety of gross blood abnormalities. The observed physiological effects obtained though the routine use of the described cells indicates that the protein simply annotated as a "RNA binding protein" or "couch potato-like protein"

in the various bioinformatics databases, is indeed a potential drug target that is particularly exploitable in the fields of immunology, cardiology, and metabolism. Virtually no *in vitro* technology, patented or otherwise, could have been used to make the direct correlation between gene and physiological function described above. *That* represents the direct scientific and commercial utility of the presently described genetically engineered ES cells. One gene down, 5,000 to go[1].

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Although approximately 30,000 genes have ostensibly been identified to date, only around 5,000 genes encode proteins from families for which "modern" chemistry has proven able to derive a therapeutically useful compound (taking into account the net productivity of the entire pharmaceutical industry over the last century). Barring a fundamental chemical breakthrough, the presently "druggable" genome generally corresponds to these 5,000 or so proteins (of which only a fraction will manifest medically significant phenotypes).